Alberti Paola (Orcid ID: 0000-0001-6106-6183)
cavaletti guido (Orcid ID: 0000-0003-4128-2406)

TOXIC MEDICATIONS IN CHARCOT-MARIE-TOOTH PATIENTS: A SYSTEMATIC REVIEW

Guido Cavaletti [1,2], Katherine Forsey [3], Paola Alberti [1,2]

[1] Experimental Neurology Unit, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy

[2] Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

[3] Charcot-Marie-Tooth Association, USA

Running title: neurotoxic drugs in CMT patients

Disclosure: Authors have nothing to disclose.

Corresponding author:

Prof. Guido Cavaletti

Experimental Neurology Unit

University of Milano-Bicocca

Via Cadore 48, I-20900 Monza (MB) – Italy

Ph: +39 02 6448 8039

Mail: guido.cavaletti@unimib.it

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jns.12566

Abstract

Background and aims

Several widely used medications, with a relevant efficacy profile, are toxic to the peripheral nervous system and an even larger number of agents are suspected to be neurotoxic. There are concerns about the use of these drugs in patients with Charcot-Marie-Tooth disease (CMT), a hereditary motor and sensory neuropathy. This review provides evidence-based updated recommendations on this clinically-relevant topic.

Methods

A systematic review of the available studies/reports written in English was performed from July-September 2022 including in the search string all reported putative neurotoxic drugs.

Results

The results of our systematic review provide evidence-based support for the statement that use of vincristine, and possibly paclitaxel, can occasionally induce an atypical, and more severe, course of drug-related peripheral neurotoxicity in CMT patients. It is therefore reasonable to recommend caution in the use of these compounds in CMT patients. However, no convincing evidence for a similar recommendation could be found for all other drugs.

Interpretation

It is important that patients with CMT are not denied effective treatments that may prolong life expectancy for cancer or improve their health status if affected by non-oncological diseases. Accurate monitoring of peripheral nerve function in CMT patients treated with any neurotoxic agent remains mandatory to detect the earliest signs of neuropathy worsening and atypical clinical courses. Neurologists monitoring CMT patients as part of their normal care package or for natural

history studies should keep detailed records of exposures to neurotoxic medications and support reporting of accelerated neuropathy progression if observed.

Key words: Charcot-Marie-Tooth disease, neurotoxicity, drugs, peripheral neuropathy, vincristine

Introduction

Several widely used medications, with a relevant efficacy profile, are toxic to the peripheral nervous system (PNS)[1] and an even larger number of agents are suspected to be neurotoxic. Concerns about the use of these drugs refer to subjects with an intact PNS, but even more to those patients with pre-existing peripheral neuropathy. Among this category, subjects with inherited neuropathies have been suggested to be at potentially higher risk[2]. Charcot-Marie-Tooth disease (CMT) is a hereditary motor and sensory neuropathy. CMT affects around 1 in 2500 people, approximately 3 million world-wide, and is the most commonly inherited neurological disorder. The overall incidence of CMT and closely related inherited peripheral neuropathies, such as hereditary neuropathy with liability to pressure palsies (HNPP), distal hereditary motor neuropathies (dHMN or HMN), and hereditary sensory (and autonomic) neuropathies (HSN or HSAN) has been estimated to be 17.69/100,000), although prevalence estimates vary across studies up to 82.3/100,000 [3, 4].

The Charcot-Marie-Tooth Association (CMTA), a leading global CMT patient advocacy organisation, has a "Medical Alert" list of potentially neurotoxic medications published on its webpage (https://www.cmtausa.org/living-with-cmt/managing-cmt/medications/). This list is also reported in a brochure that is distributed along with a "Dear Medical Professional" letter advising physicians treating CMT patients that they should consider the potential risk of prescribing drugs known to have neurotoxic properties.

This information influences patients and their treating physicians, particularly if they are not neurologists. Among the listed medications only vinca alkaloids and taxanes are considered drugs with a definite high risk if used in CMT patients. Several other drugs are reported to carry different levels of risk, ranging from "negligible or doubtful" up to "moderate to significant", contributing to a certain level of alarm regarding these drugs.

The CMTA's published list was based on a 2006 paper by Louis H. Weimer and David Podwall[2]. After an extensive literature search for reported cases of drug effects in CMT patients, Weimer and Podwall stated that in unexpectedly severe cases "the vast majority concerned excessive vincristine toxicity in patients with undiagnosed demyelinating forms of CMT", referring specifically to CMT type 1A, and most likely HNPP. However, the authors also state that "use of other agents in the significant risk category and use of vincristine in other CMT subtypes should be considered with caution" although "this recommendation is based on very limited direct evidence in patients with CMT".

Given the clear importance of a reliable information supporting or negating a higher peripheral neurotoxicity we performed a systematic review of the scientific literature regarding the severity of drug-induced side effects in inherited neuropathies to provide evidence-based updated recommendations.

Search methods

To update and revise the CMTA neurotoxic medication list, we performed a systematic review of the scientific literature searching for papers reporting only clinical data and written in English, according to the PRISMA 2020 guidelines (see Figure 1)[5].

The PubMed website was interrogated in the period July-September 2022 using a dedicated search string as follows: (drug name) AND ((Charcot Marie Tooth) OR (hereditary neuropathy) OR (hereditary neuropathy with pressure palsies) OR (Charcot-Marie-Tooth) OR (CMT) OR (CMT1) OR (CMT2) OR (DI-CMT) OR (dHMN) OR (distal hereditary motor neuropathy) OR (Dejerine-Sottas syndrome) OR (hereditary sensory neuropathy) OR (hereditary sensory and autonomic neuropathy)).

Papers were included in the review if they contained at least the description of the results of the neurological examination allowing identification of the features of worsening neuropathy and details of the time of symptom onset related to the administration of the possible neurotoxic agent. The preliminary screening was independently performed by PA, and final consensus on the inclusion/exclusion of the paper from the review was reached with GC. After selection of the papers, PA independently extracted the relevant data, and also in this case consensus on the identification of possible cases of unexpectedly severe/worsening neuropathy was reached after discussion with GC.

Drug name in the search string was not restricted to the original list by Weimer and Podwall[2], but based on the longer CMTA published list, among which antineoplastic drugs are highly represented; to the latter class we added novel anticancer drugs (i.e., Immune Checkpoint Inhibitors and antibody-drugs conjugated) if they were not all included in this list. Papers retrieved were managed using the Rayyan – Intelligent Systematic Review platform (https://www.rayyan.ai/).

Results

A total of 931 papers were retrieved. Among them, 875 were excluded from the review because they were not relevant to the scope of the review and/or not written in English language,

Regarding vincristine, the search retrieved 85 papers: 30 of them contained sufficient clinical data according to the inclusion criteria to assess the possible role of vincristine in neuropathy worsening. The papers with the most complete information were included in Table 1. For taxanes, 52 papers were retrieved, with 6 of them fulfilling the selection criteria reported above. The results for the other drugs on the CMTA neurotoxic medication list are reported in Table 3. In Table 4 we report the number of references found for all drugs other than vincristine and taxanes, which were used to build Table 3.

Vincristine

In the reported cases, vincristine use was associated with sudden worsening of peripheral neuropathy, often with prominent motor impairment and involvement of the cranial nerves. Most reports occurred in patients with CMT1A, but there are also reports in subjects with the inherited neuropathies CMT2, HNPP, CMT4 and CMT1X (Table 1). Autonomic failure (a very typical side effect of vincristine) was reported, in association with voice changes and limb weakness, in only one subject with inconclusive genetic testing for CMT, who was also treated with intrathecal methotrexate and cytarabine (Ara-C)[6].

Since the reported clinical features in most patients are not typical for vincristine-induced peripheral neurotoxicity in children or adults, an alternative diagnosis (e.g. Guillain-Barrè Syndrome [GBS]) search would have been mandatory, although made more difficult by the occasional presence of hyperproteinorrachia in CMT patients[7, 8] and the pre-existing neurophysiological changes. However, other possible explanations for the unexpected course in these patients were searched for in a minority of cases; for instance, approximately one-third of the reported cases underwent cerebrospinal fluid examination: in one case without genetic description, elevated levels of albumin with normal cell count were reported[9], while in one CMT1A patient, nerve conduction studies were consistent with severe acute sensorimotor axonal and demyelinating damage superimposed on chronic polyneuropathy[10]. A definite diagnosis could not be achieved in the patient reported by Moudgil et al.[11], but the authors suggested GBS was the most consistent hypothesis. A summary of the clinical features of the patients with suspected severe vincristine-induced peripheral neurotoxicity is reported in Table 1.

Taxanes

Increased severity of paclitaxel-induced peripheral neurotoxicity was associated with specific polymorphisms in ARHGEF10[12, 13] and SBF2[12, 14] CMT-associated genes in two different cohort studies, but these observations were not confirmed in a subsequent validation cohort[15]. One case report suggesting an atypically rapid onset of paclitaxel-related worsening of peripheral neuropathy was reported in a 60-year-old woman with a "past medical history significant for CMT", without any genetic testing available: in this case no alternative diagnosis was searched[16]. A summary of the data linking taxane administration to a possible increased severity of peripheral neurotoxicity in CMT patients is reported in Table 2.

Other neurotoxic agents

Cisplatin administration was associated with unusual rapid and severe onset of sensorimotor neurotoxicity in CMT1A patients[17]. Since it is well established that cisplatin peripheral neurotoxicity is exclusively sensory, these patients had an unexpected clinical course, but no alternative reasons for it were searched. Occasional case reports of worsening neuropathy have been published in CMT patients treated with fluoroquinolones[18] or stavudine[19], but overall these cases do not demonstrate use of these drugs is more dangerous in a CMT subject than in the general population. It is remarkable that retrospective analysis of clinical cases excluded the occurrence of more severe peripheral neurotoxicity in CMT patients treated with nitric oxide[20], and no association was found between 49 canonical CMT-associated genes and risk of severe oxaliplatin-induced peripheral neurotoxicity[21]. A summary of the results of our search excluding vincristine and taxanes, but with results potentially indicating a role in more severe neurotoxicity in CMT patients is reported in Table 3.

We also explored if Immune Checkpoint Inhibitors and antibody-drug conjugates[22] could be considered at increased risk in CMT patients, but no reports suggesting worsening of peripheral neuropathy in these patients were found.

Discussion

Apart from a set of drugs with a clear peripheral neurotoxicity profile (e.g. several anticancer chemotherapy drugs), the entire issue of drug-related peripheral nerve damage is complex and not completely settled in subjects with or without pre-existing peripheral neuropathy. Most of the drugs with a suggested, but uncertain, peripheral neurotoxicity profile including several antimicrobial, antiepileptic, anti-arrhythmic, and antineoplastic agents, have been described in small cohorts or, more frequently, in single case reports. When well-designed, large, carefully investigated series were used to confirm the preliminary observations the results were negative in most cases. This suggests no significant evidence for the claim or that the neurotoxic effect was not clinically relevant in the vast majority of patients.

The definite neurotoxic drugs have a well-established clinical phenotype and course, although the severity of PNS damage can be markedly different among treated patients. The strongest evidence for the wide range of severity can be seen in anticancer drug-treated patients[22, 23], representing the largest cohort of subjects exposed to the risk of severe drug-related peripheral neurotoxicity. In this population, it has been firmly demonstrated that the same treatment schedule administered to patients with similar demographic and oncological features could result in negligible peripheral neurotoxicity up to severely disabling and long-lasting PNS damage. The reasons for this variability have not yet been identified, and despite the possible influence of the individual's genetic background this hypothesis still lacks validation[24]. The well-established, marked variability in toxic effects on the PNS must be seriously considered in the assessment of an

individual's risk of developing more severe drug-related peripheral neurotoxicity for both those with, and without, CMT.

The possibility of marked worsening of peripheral neuropathy in CMT patients treated with neurotoxic drugs has been suggested[25], and is clinically-relevant, so it deserves to be precisely addressed to provide reliable, evidence-based safety information to patients and their treating physicians, but without raising unnecessary concerns. It is also important that patients with CMT are not denied effective treatments that may prolong life expectancy for cancer or improve their health status if affected by non-oncological diseases.

Remarkably, despite increased awareness raised by the original study by Weimer and Podwall[2], very few reports of unexpectedly severe peripheral neurotoxicity with drugs other than vincristine or paclitaxel have been subsequently reported. This observation may suggest that the possible peripheral neurotoxicity of several agents has been over-estimated.

The assumption that patients with CMT may be more susceptible to increased severity of additional toxic PNS damage is reasonable. However, for chemotherapy-induced peripheral neurotoxicity (CIPN) (one of the most likely candidates for unexpectedly severe PNS damage in CMT patients) the presence of pre-existing peripheral neuropathy is not generally considered a sufficient reason for treatment plan modification. For instance, an association has been suggested between pre-existing diabetic neuropathies and a more severe CIPN course[26, 27], but this has not led to the use of different treatment schedules in diabetic vs. non-diabetic cancer patients.

Our search was mainly based on the CMTA neurotoxic medication list and largely supported by the Weimer and Podwall review[2], so it included a large number of putative peripheral neurotoxic agents. However, it is interesting to consider the findings of a recent review on the broader topic of toxic neuropathies conducted by Peters and Staff[1]. In their paper, the authors limit the list of definite

peripheral neurotoxic drugs to three main classes (antimicrobials, antiretrovirals, and anticancer chemotherapy agents), plus a few additional miscellaneous compounds, thus markedly reducing the number of putative "dangerous" agents based on the most recent scientific evidence.

Among antimicrobials they list ethambutol, linezolid, fluoroquinolones, dapsone and metronidazole. Stavudine, didanosine, and zalcitabine are antiretroviral toxic agents on the PNS. Platinum-based drugs, vinca alkaloids, taxanes, epothilones, eribulin, thalidomide, bortezomib, vedotins, and checkpoint inhibitors are the anticancer drugs with a more well-established peripheral neurotoxicity profile. In their review, Peters and Staff also include in the list of peripheral neurotoxic agents nitrous oxide, phenytoin, and vitamin B6. Although this list is probably incomplete (for instance, they omitted amiodarone, an effective antiarrhythmic drug that can induce sensorimotor neuropathy and optic nerve damage), it provides support for a limitation to only drugs with strong evidence for peripheral neurotoxic effects.

The results of our systematic review provide evidence-based support for the statement that use of vincristine, and possibly paclitaxel, can occasionally induce an atypical, and more severe, course of drug-related peripheral neurotoxicity in CMT patients. It is therefore reasonable to recommend caution in the use of these compounds in CMT patients. However, no convincing evidence for a similar recommendation could be found for all the other drugs, including those indicated as being associated with moderate to significant risk in the current CMTA neurotoxic medications list. In fact, despite the well-documented neurotoxic status of some of the listed medications, and the severity of their neurotoxicity being a remarkable and a potentially dose-limiting side effect, no evidence for a more severe course in CMT patients has been demonstrated.

It is possible that cases of unexpectedly severe worsening of peripheral neuropathy in CMT patients have not been reported in the scientific literature, and therefore have not appeared in our search. Accurate monitoring of peripheral nerve function in CMT patients treated with any

neurotoxic agent remains mandatory to detect the earliest signs of neuropathy worsening and atypical clinical courses. If detected, appropriate measures to minimize PNS damage severity should be rapidly enforced. Neurologists monitoring CMT patients as part of their normal care package or for natural history studies should keep detailed records of exposures to neurotoxic medications and support reporting of accelerated neuropathy progression if observed.

Moreover, a prospective study of a well-characterized series of CMT patients treated with established or putative neurotoxic drugs could achieve solid evidence in favor or against an increased risk in this specific population.

Acknowledgements

The authors gratefully acknowledge the critical revision of the search results provided by Davide Pareyson and Alexander M Rossor.

This study was conceived and supported by a research grant from the Charcot-Marie-Tooth Association.

The results of this systematic review have been presented at the 2023 Peripheral Nerve Society meeting (Copenhagen, 17-20 June 2023)

References

1. Peters J, Staff NP. Update on Toxic Neuropathies. Curr Treat Options Neurol 2022;24:203-216.

2. Weimer LH, Podwall D. Medication-induced exacerbation of neuropathy in Charcot Marie Tooth disease. J Neurol Sci 2006;242:47-54.

3. Ma M, Li Y, Dai S, et al. A meta-analysis on the prevalence of Charcot-Marie-Tooth disease and related inherited peripheral neuropathies. J Neurol 202 ;270:2468-2482.

4. Barreto LC, Oliveira FS, Nunes PS, et al. Epidemiologic Study of Charcot-Marie-Tooth Disease: A Systematic Review. Neuroepidemiology 2016;46:157-165.

5. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.

6. Trobaugh-Lotrario AD, Smith AA, Odom LF. Vincristine neurotoxicity in the presence of hereditary neuropathy. Med Pediatr Oncol 2003;40:39-43.

7. Pareyson D, Testa D, Morbin M, et al. Does CMT1A homozygosity cause more severe disease with root hypertrophy and higher CSF proteins? Neurology 2003;60:1721-1722.

8. Taniguchi T, Ando M, Okamoto Y, et al. Genetic spectrum of Charcot-Marie-Tooth disease associated with myelin protein zero gene variants in Japan. Clin Genet 2021;99:359-375.

9. Hogan-Dann CM, Fellmeth WG, McGuire SA, Kiley VA. Polyneuropathy following vincristine therapy in two patients with Charcot-Marie-Tooth syndrome. JAMA 1984;252:2862-2863.

10. Jariwal R, Shoua B, Sabetian K, Natarajan P, Cobos E. Unmasking a Case of Asymptomatic Charcot-Marie-Tooth Disease (CMT1A) With Vincristine. J Investig Med High Impact Case Rep 2018;6:2324709618758349.

11. Moudgil SS, Riggs JE. Fulminant peripheral neuropathy with severe quadriparesis associated with vincristine therapy. Ann Pharmacother 2000;34:1136-1138.

12. Beutler AS, Kulkarni AA, Kanwar R, et al. Sequencing of Charcot-Marie-Tooth disease genes in a toxic polyneuropathy. Ann Neurol 2014;76:727-737.

13. Boora GK, Kanwar R, Kulkarni AA, et al. Testing of candidate single nucleotide variants associated with paclitaxel neuropathy in the trial NCCTG N08C1 (Alliance). Cancer Med 2016;5:631-639.

14. Schneider BP, Lai D, Shen F, et al. Charcot-Marie-Tooth gene, SBF2, associated with taxane-induced peripheral neuropathy in African Americans. Oncotarget 2016;7:82244-82253.

15. Chen Y, Fang F, Kidwell KM, et al. Genetic variation in Charcot-Marie-Tooth genes contributes to sensitivity to paclitaxel-induced peripheral neuropathy. Pharmacogenomics 2020;21:841-851.

16. Martino MA, Miller E, Grendys EC. The administration of chemotherapy in a patient with Charcot-Marie-Tooth and ovarian cancer. Gynecol Oncol 2005;97:710-712.

17. Yerushalmi R, Levi I, Wygoda M, Ifergane G, Wirguin I. Are platinum-based chemotherapeutic drugs safe for patients with Charcot-Marie-Tooth disease? J Peripher Nerv Syst 2007;12:139-141.

18. Panas M, Karadima G, Kalfakis N, Vassilopoulos D. Hereditary neuropathy unmasked by levofloxacin. Ann Pharmacother 2011;45:1312-1313.

19. Miller RF, Bunting S, Sadiq ST, Manji H. Peripheral neuropathy in patients with HIV infection: consider dual pathology. Sex Transm Infect 2002;78:462-463.

20. Isbister GK, Burns J, Prior F, Ouvrier RA. Safety of nitrous oxide administration in patients with Charcot-Marie-Tooth disease. J Neurol Sci 2008;268:160-162.

21. Le-Rademacher JG, Lopez CL, Kanwar R, et al. Neurological safety of oxaliplatin in patients with uncommon variants in Charcot-Marie-tooth disease genes. J Neurol Sci 2020;411:116687.

22. Alberti P, Salvalaggio A, Argyriou AA, et al. Neurological Complications of Conventional and Novel Anticancer Treatments. Cancers 2022;14:6088.

23. Tay CG, Lee VWM, Ong LC, Goh KJ, Ariffin H, Fong CY. Vincristine-induced peripheral neuropathy in survivors of childhood acute lymphoblastic leukaemia. Pediatr Blood Cancer 2017;64.

24. Argyriou AA, Bruna J, Genazzani AA, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity: management informed by pharmacogenetics. Nat Rev Neurol 2017;13:492-504.

25. Weimer LH, Sachdev N. Update on medication-induced peripheral neuropathy. Curr Neurol Neurosci Rep 2009;9:69-75.

26. Gu J, Lu H, Chen C, et al. Diabetes mellitus as a risk factor for chemotherapy-induced peripheral neuropathy: a meta-analysis. Support Care Cancer 2021;29:7461-7469.

27. Molassiotis A, Cheng HL, Leung KT, et al. Risk factors for chemotherapy-induced peripheral neuropathy in patients receiving taxane- and platinum-based chemotherapy. Brain Behav 2019;9:e01312.

28. Ajitsaria R, Reilly M, Anderson J. Uneventful administration of vincristine in Charcot-Marie-Tooth disease type 1X. Pediatr Blood Cancer 2008;50:874-876.

29. Aghajan Y, Yoon JM, Crawford JR. Severe vincristine-induced polyneuropathy in a teenager with anaplastic medulloblastoma and undiagnosed Charcot-Marie-Tooth disease. BMJ Case Rep 2017;2017:bcr2016218981.

30. Chauncey TR, Showel JL, Fox JH. Vincristine neurotoxicity. JAMA 1985;254:507.

31. Chauvenet AR, Shashi V, Selsky C, et al. Vincristine-induced neuropathy as the initial presentation of charcot-marie-tooth disease in acute lymphoblastic leukemia: a Pediatric Oncology Group study. J Pediatr Hematol Oncol 2003;25:316-320.

32. Cil T, Altintas A, Tamam Y, Battaloğlu E, Isikdogan A. Low dose vincristine-induced severe polyneuropathy in a Hodgkin lymphoma patient: a case report (vincristine-induced severe polyneuropathy). J Pediatr Hematol Oncol 2009;31:787-789.

33. Dickerhoff R, Lindner W, Scheiber W. Severe vincristine neurotoxicity in a patient with Charcot-Marie-Tooth disease. Pediatr Hematol Oncol 1988;5:61-64.

34. Gogou M, Pavlidou E, Pavlou E, et al. Charcot-Marie-Tooth 1A concurrent with anaplastic ependymoma in a toddler: when an acute event unmasks a chronic condition. Turk J Pediatr 2019;61:428-430.

35. Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. Cancer 1996;77:1356-1362.

36. Hildebrandt G, Holler E, Woenkhaus M, et al. Acute deterioration of Charcot-Marie-Tooth disease IA (CMT IA) following 2 mg of vincristine chemotherapy. Ann Oncol 2000;11:743-747.

37. Ichikawa M, Suzuki D, Inamoto J, et al. Successful alternative treatment containing vindesine for acute lymphoblastic leukemia with Charcot-Marie-Tooth disease. J Pediatr Hematol Oncol 2012;34:239-241.

38. Kalfakis N, Panas M, Karadima G, Floroskufi P, Kokolakis N, Vassilopoulos D. Hereditary neuropathy with liability to pressure palsies emerging during vincristine treatment. Neurology 2002;59:1470-1471.

39. Kissoon T, Gururangan S, Sladky J. Acute neurotoxicity following vincristine due to Charcot-Marie-Tooth disease in a young child with medulloblastoma. Neurooncol Pract 2019;6:179-184.

40. Mercuri E, Poulton J, Buck J, et al. Vincristine treatment revealing asymptomatic hereditary motor sensory neuropathy type 1A. Arch Dis Child 1999;81:442-443.

41. Nakamura T, Hashiguchi A, Suzuki S, Uozumi K, Tokunaga S, Takashima H. Vincristine exacerbates asymptomatic Charcot-Marie-tooth disease with a novel EGR2 mutation. Neurogenetics 2012;13:77-82.

42. Neumann Y, Toren A, Rechavi G, et al. Vincristine treatment triggering the expression of asymptomatic Charcot-Marie-Tooth disease. Med Pediatr Oncol 1996;26:280-283.

43. Naumann R, Mohm J, Reuner U, Kroschinsky F, Rautenstrauss B, Ehninger G. Early recognition of hereditary motor and sensory neuropathy type 1 can avoid life-threatening vincristine neurotoxicity. Br J Haematol 2001;115:323-325.

44. Nishikawa T, Kawakami K, Kumamoto T, et al. Severe neurotoxicities in a case of Charcot-Marie-Tooth disease type 2 caused by vincristine for acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2008;30:519-521.

45. Olek MJ, Bordeaux B, Leshner RT. Charcot-Marie-Tooth disease type I diagnosed in a 5-year-old boy after vincristine neurotoxicity, resulting in maternal diagnosis. J Am Osteopath Assoc 1999;99:165-167.

46. Orejana-García AM, Pascual-Huerta J, Pérez-Melero A. Charcot-Marie-Tooth disease and vincristine. J Am Podiatr Med Assoc 2003;93:229-233.

47. Porter CC, Carver AE, Albano EA. Vincristine induced peripheral neuropathy potentiated by voriconazole in a patient with previously undiagnosed CMT1X. Pediatr Blood Cancer 2009;52:298-300.

48. Schiavetti A, Frascarelli M, Uccini S, Novelli A. Vincristine neuropathy: neurophysiological and genetic studies in a case of Wilms tumor. Pediatr Blood Cancer 2004;43:606-609.

49. Sy A, Cheng J, Cooper R, Mueller L. Heterozygosity for CMT Type 4 Predicts a Severe Vincristine-induced Polyneuropathy Phenotype: A Case Report and Review of Literature. J Pediatr Hematol Oncol 2019;41:e41-e43.

50. Boora GK, Kulkarni AA, Kanwar R, et al. Association of the Charcot-Marie-Tooth disease gene ARHGEF10 with paclitaxel induced peripheral neuropathy in NCCTG N08CA (Alliance). J Neurol Sci 2015;357:35-40.

51. Kourie HR, Mavroudakis N, Aftimos P, Piccart M. Charcot-Marie-Tooth hereditary neuropathy revealed after administration of docetaxel in advanced breast cancer. World J Clin Oncol 2017;8:425-428.

52. Herskovitz S, Loh F, Berger AR, Kucherov M. Erythromelalgia: association with hereditary sensory neuropathy and response to amitriptyline. Neurology 1993;43:621-622.

53. Budure AN, Winquist E, Palma D, Correa RJM. Successful treatment of nasopharyngeal cancer using radiotherapy with concurrent cetuximab in a patient with Charcot-Marie-Tooth disease. BMJ Case Rep 2019;12:e228956.

54. Cowie F, Barrett A. Uneventful administration of cisplatin to a man with X-linked Charcot-Marie-Tooth disease (CMT). Ann Oncol 2001;12:422.

55. Kikukawa Y, Hata H, Ueda M, et al. Successful Treatment of Amyloid Light-chain Amyloidosis in a Charcot-Marie-Tooth Disease Patient with Lenalidomide, Cyclophosphamide, and Dexamethasone. Intern Med 2016;55:2707-2712.

56. Wang C, Guan YZ, Cai QQ, Su W, Zhou DB, Li J. Rapidly Progressive Polyneuropathy in a Patient With Monoclonal Gammopathy: A Case Report of POEMS Syndrome and Beyond. Medicine (Baltimore) 2016;95:e3453.

57. Adhikary SD, Korula PJ. The role of monitoring the depth of anesthesia in a case of hereditary sensory and autonomic neuropathy (Riley Day syndrome). Paediatr Anaesth 2007;17:402-403.

58. Greenberg RS, Parker SD. Anesthetic management for the child with Charcot-Marie-Tooth disease. Anesth Analg 1992;74:305-307.

59. Kotani N, Hirota K, Anzawa N, Takamura K, Sakai T, Matsuki A. Motor and sensory disability has a strong relationship to induction dose of thiopental in patients with the hypertropic variety of Charcot-Marie-Tooth syndrome. Anesth Analg 1996;82:182-186.

60. Naguib M, Samarkandi AH. Response to atracurium and mivacurium in a patient with Charcot-Marie-Tooth disease. Can J Anaesth 1998;45:56-59.

61. Prabhu S, Fortier K, Newsome L, Reebye UN. Office-Based Anesthetic and Oral Surgical Management of a Child With Hereditary Sensory Autonomic Neuropathy Type IV: A Case Report. Anesth Prog 2018;65:181-186.

62. Maghsoodi N, Crook MA. A case of charcot-marie-Tooth (CMT) disease with hypercholesterolaemia and statin side-effects: A case report and literature review. J Clin Neurosci 2017;38:57-59.

Table 1. Vincristine and hereditary neuropathies

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
Ajitsaria et al. 2008 [28]	Case report	CMT1X	None	Not stated	No	No
Aghajani et al. 2017 [29]	Case report	CMT1A	Cranial nerve involvement, motor worsening (limbs)	Not stated	No	Demyelinating and axonal sensory-motor polyneuropathy
Chauncey et al. 1985 [30]	Case report	Undetermined	Motor and sensory worsening (limbs)	6 days	Normal	Mixed severe polyneuropathy with denervation at EMG
Chauvenet et al. 2003 [31]	Clinical study	4 patients affected by CMT1A and 1 by CMT2 (patient 3); the latter was not confirmed by genetic testing	Motor and sensory worsening (limbs)	Patient 1: onset at day 20 from 1st dosage, worsening at day 22. Patient 3: 7 weeks after 1st cycle. Patient 4: 13 weeks after 1st cycle. Patient 5: day 29 after 1st cycle	No	Patient 3: "data compatible with CMT". Patient 5: mixed polyneuropathy

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
Cil et al. 2009 [32]	Case report	CMT1A	Motor and sensory worsening (limbs)	7 days	No	Severe acute polyneuropathy (no recordable SAP or CMAP) with denervation at EMG
Dickerhoff et al. 1988 [33]	Case report	Unspecified	Cranial nerves involvement, motor worsening (limbs)	3 days after last injection	No	No
Gogou et al 2019 [34]	Case report	CMT1A	Sensory worsening (limbs)	Not specified	No	Demyelinating polyneuropathy
Graf et al. 1996 [35]	Retrospective case series	CMT1A	Patient 1: motor and sensory worsening (limbs). Patient 2: motor and sensory worsening (limbs). Patient 3: cranial nerve involvement and motor worsening (limbs)	Patient 1: 3 weeks after 1st cycle. Patient 2: 10 days. Patient 3: not specified.	No	Mainly demyelinating polyneuropathy

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
Hildebrandt et al. 2000 [36]	Case report	CMT1A	Cranial nerve involvement, motor and sensory worsening (limbs)	10 days after 1st cycle	Normal; elevated IgG antibody titre for Borrellia burgdorferi, but IgM negative	Mixed with acute denervation at EMG
Hogan-Dann et al. 1984 [9]	Case reports (n=2)	Unspecified	Cranial nerve involvement, motor and sensory worsening (limbs)	Patient 1: 2 days after the 2nd dose. Patient 2: 14 days after the 2nd dose	Patient 1: protein 105 mg/dl, acellular, glucose 64 mg/dl. Patient 2: protein 30 mg/dl, 65mg/dl glucose, acellular.	Demyelinating polyneuropathy for both patients
Ichikawa et al. 2012 [37]	Case report	CMT1A	Motor and sensory worsening (limbs)	3 weeks after last dose	normal	Demyelinating polyneuropathy

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
Jariwal et al. 2018 [10]	Case report	CMT1A	Motor/sensory worsening (limbs)	4 days	No	Severe axonal and demyelinating polyneuropathy with denervation at EMG
Kalfakis et al. 2002 [38]	Case report	HNPP	Motor/sensory worsening (limbs)	2 weeks after 1st cycle	Normal	Severe subacute sensorimotor axonal and demyelinating polyneuropathy with active denervation at EMG
Kissoon et al. 2019 [39]	Case report	CMT1A	Motor/sensory worsening (limbs)	4 weeks after 1st cycle	Elevated protein without pleocytosis or malignant cells	Severe subacute sensorimotor axonal and demyelinating polyneuropathy
Mercuri et al. 1999 [40]	Case report	CMT1A	Cranial nerve involvement, motor worsening (limbs)	Not stated	No	Demyelinating polyneuropathy

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
Moudgil et al. 2000 [11]	Case report	Undefined	Sensory and motor worsening (limbs)	2 weeks after the last VCR dose	WBC count 1/mm3, protein 66 mg/dl, and normal glucose	Demyelinating polyneuropathy, with some axonal features. Active denervation at EMG
Nakamura et al. 2012 [41]	Case report	Novel mutation in the EGR2 gene	Sensory/motor worsening (limbs)	Not stated	No	Demyelinating polyneuropathy complicated by axonal sensorimotor polyneuropathy
Neumann et al. 1996 [42]	Case report	CMT1A	Motor/sensory worsening (limbs)	Not stated	No	No
Naumann et al. 2001 [43]	Case report	CMT1A	Motor worsening (limbs)	3 weeks	No	Demyelinating polyneuropathy
Nishikawa et al. 2008 [44]	Case report	CMT2 was diagnosed based on the physical examination and	Motor worsening	Not stated	Cell count 5/mL, protein 39 mg/dl, glucose 46 mg/dl.	Axonal polyneuropathy

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
		NCS/EMG. Genetic studies including PMP22, P0, NEFL, MFN2, HSPB1, and HSPB8 were normal			Immunoglobulin G index 0.344; MBP and antiganglioside antibodies were negative	
Olek et al.1999 [45]	Case report	Unspecified. Assigned as CMT1 based on NCS	Cranial nerve involvement, motor worsening (limbs)	5 days after last VCR dose	Protein 93 mg/dl (normal for that laboratory normative data), glucose 62 mg/dl, WBC 4/mm3 (79% lymphocytes, 1% monocytes). Negative cultures.	Axonal polyneuropathy with active denervation at EMG

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
Orejana-García et al. 2003 [46]	Case report	Unspecified. Assigned as CMT1 based on NCS	Motor/sensory worsening (limbs)	Not stated	No	Sensorimotor polyneuropathy. Demyelination reported in nerve biopsy
Porter et al. 2009 [47]	Case report	CMT1X	Motor worsening (limbs)	Not stated	No	Normal
Schiavetti et al. 2004 [48]	Case report	CMT1A	Cranial nerves involvement, sensory/motor worsening (limbs)	After 1st dose (mild), after 2nd dose (severe)	No	Axonal neuropathy, motor greater than sensory. Active denervation at EMG
Sy et al. 2019 [49]	Case report	Heterozygous missense mutation in the PRX gene on chromosome 19q 13.2. Classified as a	Sensory/motor worsening (limbs)	After 10 doses developed first symptoms. Received the 1st cycle while intubated for the severity of the oncological situation	No	No

Reference	Type of study	Genotype	Main findings potentially associated with vincristine administration	Days after VCR administration	CSF	NCS/EMG related to the neuropathy worsening
		genetic carrier of CMT4				
Trobaugh-Lotrario et al. 2003 [6]	Case report	Coding regions of the CX32 and P0 genes showed no mutations. Additional tests for CMT1A and HNPP were inconclusive	Cranial nerves, motor worsening (limbs), uncertain sensory worsening (limbs)	Not stated	Acellular, protein 202 mg/dl	Mixed polyneuropathy

VCR = vincristine, CSF = cerebrospinal fluid, NCS = nerve conduction studies, EMG = electromyography, CMT = Charcot-Marie-Tooth neuropathy (different subtypes identified by specific number/letter), SAP = amplitude of the sensory potential, CMAP = compound muscular amplitude potential, HNPP = hereditary neuropathy with pressure palsy, WBC = white blood cell, EGR2 = early growth response 2, PMP22 = peripheral myelin protein 22, P0 = myelin protein 0, NEFL = neurofilament light chain, MFN2 = mitofusin 2, HSPB1 = heat shock protein family B (Small) Member 1, HSPB8 = heat shock protein family B (small) member 8, MBP = myelin basic protein, PRX = periaxin, CX32 = connexin 32.

Table 2. Taxanes and hereditary neuropathies.

Reference	Drug	Type of study	Genotype	Main findings potentially associated with paclitaxel administration	Days after PTX administration	CSF	NCS/EMG related to the neuropathy worsening
Beutler et al. 2014 [12]	PTX	Clinical study – retrospective	119 (of 269) patients were identified from the 2 ends of the polyneuropathy phenotype distribution: patients that were most and least susceptible to PTX polyneuropathy. Heterozygous variants in the recessive CMT gene PRX were enriched in patients who were susceptible to CIPN but not in controls. Genetic variation in ARHGEF10, which was thought to be a CMT gene at the time of the study, was highly significantly associated with CIPN. Three nonsynonymous recurrent single nucleotide variants contributed to the ARHGEF10 signal: rs9657362 (strongest effect), rs2294039, and rs17683288.	The results reveal an association of gene allelic variability with susceptibility to CIPN	Not stated	No	No

Boora et al 2015 [50]	PTX	Clinical study – retrospective	A study-wide, Rasch-type model was used to perform extreme phenotyping in 138 eligible patients	A significant association of ARHGEF10 with CIPN was found	Not stated	No	No
Chen et al. 2020 [15]	PTX	Clinical study – retrospective	Putative genetic predictors in hereditary neuropathy genes (*ARHGEF10, SBF2, FGD4)* in 58 patients were investigated	None of the genetic predictors were associated with polyneuropathy increases sensitivity	Not stated	No	No
Kourie et al. 2017 [51]	DOCE	Case report	CMT1A	Sensory and motor worsening (limbs)	3 months after completion of 6 cycles	No	No
Martino et al. 2005 [16]	PTX/DOCE	Case report	Patient known for CMT before starting chemotherapy (unspecified type)	Patient developed a distal sensory and motor neuropathy after first treatment with carboplatin and PTX and was unable to walk, write, or drive. Upon changed from PTX to DOCE symptoms dramatically improved.	7 days	No	No

chneider et al. 2016 [14]	PTX	Clinical study – retrospective	Whole exome sequencing was performed using germline DNA from 213 patients who received a standard dose and schedule of PTX. Cases were defined as those with either grade 3-4 or grade 2-4 CIPN and were compared to controls that were not reported to have experienced CIPN. SBF2 was significantly associated with CIPN and five variants were predicted to be deleterious	Rare heterozygous variants in SBF2 predicted an increased risk of CIPN in patients receiving PTX	Not stated	No	No

PTX = paclitaxel, CSF = cerebrospinal fluid, NCS = nerve conduction studies, EMG = electromyography, CMT = Charcot-Marie-Tooth neuropathy (different subtypes identified by specific number/letter), PRX = periaxin, CIPN = chemotherapy-induced peripheral neurotoxicity, ARHGEF10 = Rho Guanine Nucleotide Exchange Factor 10, SBF2 = SET binding factor 2, FGD4 = FYVE, RhoGEF and PH domain containing 4, or frabin, DOCE = docetaxel.

Table 3. Other drugs and hereditary neuropathies.

Drug	Reference	Type of study	Genotype	Cranial nerves involvement / motor worsening / sensory worsening / autonomic involvement (or combination)	CSF	NCS/EMG related to the neuropathy worsening
Amitriptyline	Herskovitz et al. 1993 [52]	Case report	Unspecified	No specific risk is reported.	No	No
Cetuximab	Budure et al. 2019 [53]	Case report	CMT2A	No neuropathy worsening (CMT known before treatment)	No	No
Cisplatin	Cowie et al. 2001 [54]	Case report	CMTX	No neuropathy worsening (CMT known before treatment)	No	No
Cisplatin	Gogou et al. 2019 [34]	See table 1	See table 1	See table 1	See table 1	See table 1
Cisplatin	Yerushalmi et al. 2007 [17]	Case report	Undefined	Sensory and motor worsening (limbs)	No	Demyelinating polyneuropathy
Fluroquinolones	Panas et al. 2011 [18]	Case report	Undefined	Motor and sensory worsening (limbs)	No	Mixed demyelinating and axonal

Drug	Reference	Type of study	Genotype	Cranial nerves involvement / motor worsening / sensory worsening / autonomic involvement (or combination)	CSF	NCS/EMG related to the neuropathy worsening
						sensorimotor polyneuropathy
Lenalidomide	Kikukawa 2016 et al. [55]	Case report	Not specified	No neuropathy worsening (CMT known before treatment)	No	No
Lenalidomide	Wang 2016 et al. [56]	Case report	CMT2A2	The patients had POEMS before starting treatment. Genetic neuropathy was revealed during diagnostic work-up.	No	No
Nitrous oxide	Adhikary et al. 2007 [57]	Case report	HSAN, Riley-Day syndrome	No specific risk is reported.	No	No
Nitrous oxide	Greenberg et al. 1992 [58]	Case series (n=7)	Unspecified	No specific risk is reported.	No	No
Nitrous oxide	Isbistier et al. 2008 [20]	Review	Unspecified	Systematic review including 41 exposures to therapeutically inhaled nitrous oxide as maintenance for general anaesthesia with	No	No

Drug	Reference	Type of study	Genotype	Cranial nerves involvement / motor worsening / sensory worsening / autonomic involvement (or combination)	CSF	NCS/EMG related to the neuropathy worsening
				no reports of adverse effects or worsening of CMT neuropathy.		
Nitrous oxide	Kotani et al. 1996 [59]	Clinical study –	CMT	No specific risk is reported	No	No
Nitrous oxide	Naguib et al. 1998 [60]	Case report	Not specified	No specific risk is reported	No	No
Nitrous oxide	Prabhu et al. 2018 [61]	Case series	HSAN IV	No specific risk is reported	No	No
Oxaliplatin	Le-Rademacher et al. 2020 [21]	Clinical study - retrospective	353 patients, 49 canonical CMT-associated genes analysed	No specific risk is reported	No	No
Statin	Maghsoodi et al. 2017 [62]	Case report	CMT1A	Statins were discontinued for muscle intolerance	No	No

Drug	Reference	Type of study	Genotype	Cranial nerves involvement / motor worsening / sensory worsening / autonomic involvement (or combination)	CSF	NCS/EMG related to the neuropathy worsening
Stavudine	Miller et al. 2002 [19]	Case reports (n=2)	Patient 1: HNPP Patient 2: CMT1A	Patient 1: mild sensory worsening (limbs) Patient 2: sensory worsening (pain)	No	Patient 1: sensorimotor (predominantly sensory) peripheral neuropathy with demyelinating features, attributed to HNPP only by the authors. Patient 2: Nerve conduction studies and an EMG showed evidence of a mixed sensorimotor demyelinating neuropathy.

Drug	Reference	Type of study	Genotype	Cranial nerves involvement / motor worsening / sensory worsening / autonomic involvement (or combination)	CSF	NCS/EMG related to the neuropathy worsening
Thalidomide	Kikukawa et al. 2016 [55]	Case report	CMT, genotype n/a	Thalidomide was not administered since CMT was already known. Patient received lenalidomide and she experienced no progression of either muscle weakness or amyotrophy, and sensory impairment.	No	No
Thalidomide	Wang et al. 2016 [56]	Case report	CMT2A2	Patient was wheelchair bound due to POEMS. Thalidomide was not administered since CMT was already known. Patient received lenalidomide with amelioration of both sensory and motor symptoms.	No	Partial improvement of demyelinating polyneuropathy after treatment with lenalidomide.

CSF = cerebrospinal fluid, NCS = nerve conduction studies, EMG = electromyography, CMT = Charcot-Marie-Tooth neuropathy (different subtypes identified by specific number/letter), POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes, HSAN = hereditary sensory and autonomic neuropathy, HNPP = hereditary neuropathy with pressure palsy.

Table 4. Summary of the entry found to build Table 3.

Drug	Retrieved papers	Relevant papers
5-fluorouracil	24	0
Adriamicyn	0	0, but overlap with vincristine in Hildebrant 2000 (see Table 1)
Alcohol	461	0 (2 case reports not in English)
Allopurinol	0	0
Almitrine	1	0
Alpha interferon	18	0
Amiodarone	7	0
Amitriptyline	4	1
Antibody-drug conjugates that are not present in the CMTA list ("antibody drug conjugates", disitamab vedotin, tisotumab vedotin, inotuzumab vedotin, polantuzumab vedotin-piiq, ado-trastuzumab emtansine, gemtuzuman ozogamicin, belantamab mafodotin)	1	0
Arsenic trioxide	7	0
Bortezomib	5	0
Brentuzimab vedotin	0	0
Cabazitaxel	0	0

Cetuximab	2	1
Chloroquine	2	0
Chlorprothixene	0	0
Cimetidine	24	0
Cisplatin	31	3
Clioquinil	0	0
Clofibrate	1	0
Colchicine	2	0
Cyclosporin A	12	0
Cytarabine	4	0, but overlap with vincristine in Nishikawa 2008 (see Table 1)
Dapsone	2	0
Dichloroacetate	3	0
Didanosine	0	0
Disulfiram	2	0
Enalapril	2	0
Eribulin	0	0
Ethambutol	23	0, but overlap with vincristine in Fonkem 2013 (see Table 1)
Etoposide	13	0, but overlap with vincristine in Nishikawa 2008 (see Table 1)

Gemcitabine	9	0
Glutethimide	0	0
Gold salts/gold salt	2	0
Griseofulvin	1	0
Hexamethylmelamine	0	0
Hydralazine	0	0
Ifosphamide	0	0
Infliximab	6	0
Immune Checkpoint Inhibitors not included in CMTA list ("immune check point inhibitors", cemiplimab, atezolizumb, durvalumab)	6	0
Ipilimumab	0	0
Ixabepilone	0	0
Lansoprazole	0	0
Lenaflunomide	0	0
Lenalidomide	3	2
(levofloxacin OR ciprofloxacin OR moxifloxacin OR ofloxacin OR gemifloxacin OR delafloxacin OR fluoroquinolones)	3	1
Lithium	10	0

Mefloquine	0	0
Metroinidazole	0	0
Misoinidazole	0	0
Nitrofurantoin	5	0
Nitrous oxide	13	6
Nivolumab	0	0
Omeprazole	1	0
Oxaliplatin	9	1
Pembrolizumab	1	0
Penicillamine	5	0
Perhexiline	2	0
Phenelzine	1	0
Phenythoin	0	0
Podophyllin resin	1	0
Pomalidomide	0	0
Propafenone	0	0
Pyridoxine	9	0
Sertraline	0	0

((statin) OR (statins) OR (atorvastatin) OR (Fluvastatin) OR (pravastatin) OR (rosuvastatin) OR (simvastatin))	23	1
Stavudine	1	1
Sulphasalzine	0	0
((sulfonamide) OR (sulfonamides) OR (sulfadiazine) OR (sulfamethizole) OR (sulfamethoxazole) OR (sulfasalazine) OR (sulfisoxazole))	31	0
Suramin	0	0
Thalidomide	7	2
Zalcitabine	1	0
Zimeldine	0	0

Figure 1. PRISMA diagram summarizing literature search.